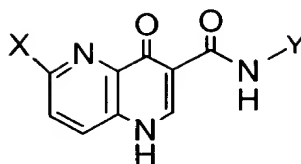


## Claims

### What is claimed is:

1. A pharmaceutical composition comprising an acetylcholinesterase inhibitor and an inverse agonist of the GABA<sub>A</sub>  $\alpha$ 1 and/or  $\alpha$ 5 receptor subtype wherein the inverse agonist has a functional efficacy at the  $\alpha$ 1 and/or  $\alpha$ 5 receptor subtypes of less than -5%, preferably less than -10%, and the efficacy measured at the  $\alpha$ 2 and  $\alpha$ 3 receptor subtypes is greater than 5% or preferably greater than 10%, and a pharmaceutically acceptable carrier, said composition being effective in the treatment of a cognitive disorder.
2. The pharmaceutical composition of claim 1, wherein the inverse agonist has a functional potency (EC<sub>50</sub> values) at the  $\alpha$ 1 and/or  $\alpha$ 5 receptor subtypes of 200 nM, preferably less than 150 nM.
3. The pharmaceutical composition of claim 1, wherein the inverse agonist has a functional efficacy at the  $\alpha$ 5 receptor subtype of less than -5%, preferably less than -10%, and the efficacy measured at the  $\alpha$ 1,  $\alpha$ 2 and  $\alpha$ 3 receptor subtypes is greater than 5% or preferably greater than 10%.
4. The pharmaceutical composition of claim 3, wherein the inverse agonist has a functional potency (EC<sub>50</sub> values) at the  $\alpha$ 5 receptor subtype of 200 nM, preferably less than 150 nM.
5. The pharmaceutical composition of claim 1, wherein the inverse agonist at the  $\alpha$ 1 and/or  $\alpha$ 5 receptor subtypes has a binding K<sub>i</sub> of 100 nM, preferably less than 30 nM.
6. A pharmaceutical composition comprising a pharmaceutically acceptable carrier, a GABA<sub>A</sub> inverse agonist, and an acetylcholinesterase inhibitor, wherein said GABA<sub>A</sub> inverse agonist is selected from a compound of Formula I below:



I

wherein:

X is hydrogen, halogen,  $-OR_1$ ,  $NR_2R_3$ ,  $C_1-C_6$  alkyl optionally substituted with up to three groups selected independently from halogen and hydroxy, or  $-NR_2R_3$ ; or

X is phenyl, naphthyl, 1-(5,6,7,8-tetrahydro)naphthyl or 4-(1,2-dihydro)indenyl, pyridinyl, pyrimidyl, isoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, benzofuranyl, benzothieryl, each of which is optionally substituted with up to three groups selected from halogen,  $C_1-C_6$  alkyl,  $C_1-C_4$  alkoxy,  $C_1-C_6$  alkylthio, hydroxy, amino, mono or di( $C_1-C_6$ ) alkylamino, cyano, nitro, trifluoromethyl; or

X represents a carbocyclic group ("the X carbocyclic group") containing from 3 - 7 members, up to two of which members are optionally hetero atoms selected from oxygen and nitrogen, where the X carbocyclic group is optionally substituted with one or more groups selected from halogen, ( $C_1-C_6$ )alkoxy, mono- or di( $C_1-C_6$ )alkylamino, sulfonamide, aza( $C_3-C_7$ )cycloalkyl, ( $C_3-C_7$ )cycloalkylthio, ( $C_1-C_6$ )alkylthio, phenylthio, or a heterocyclic group; and

Y is lower alkyl having 1 - 8 carbon atoms optionally substituted with up to two groups selected from halogen, ( $C_1-C_6$ )alkoxy, mono- or di( $C_1-C_6$ )alkylamino, sulfonamide, aza( $C_3-C_7$ )cycloalkyl, ( $C_3-C_7$ )cycloalkylthio, ( $C_1-C_6$ )alkylthio, phenylthio, a heterocyclic group,  $-OR_4$ ,  $-NR_5R_6$ ,  $SR_7$ , or aryl; or

Y is a carbocyclic group ("the Y carbocyclic group") having from 3 - 7 members atoms, where up to three of which members are optionally hetero atoms selected from oxygen and nitrogen and where any member of the Y carbocyclic group is optionally substituted with halogen,  $-OR_4$ ,  $-NR_5R_6$ ,  $SR_7$ , aryl or a heterocyclic group; and

$R_1$  is hydrogen, lower alkyl having 1 - 6 carbon atoms, or cycloalkyl having 3 - 7 carbon atoms, where each alkyl may be optionally substituted with  $-OR_4$  or  $-NR_5R_6$ ;

$R_2$  and  $R_3$  are the same or different and represent hydrogen, lower alkyl optionally mono- or disubstituted with alkyl, aryl, halogen, or mono- or di-lower alkyl;

5 cycloalkyl having 3 – 7 carbon atoms optionally mono or disubstituted with halogen, alkoxy, or mono- or di- lower alkyl; or

$R_4$  is as defined for  $R_1$ :

$R_5$  and  $R_6$  carry the same definitions as  $R_2$  and  $R_3$ , respectively;

10 R<sub>7</sub> is hydrogen, lower alkyl having 1 – 6 carbon atoms, or cycloalkyl having 3 – 7 atoms; and

R<sub>8</sub> is lower alkyl having 1 – 6 carbon atoms, cycloalkyl having 3 – 7 carbon atoms, or optionally substituted phenyl,

or a pharmaceutically acceptable prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug,

15 said composition being effective in the treatment of a cognitive disorder.

7. A pharmaceutical composition comprising a pharmaceutically acceptable carrier, a GABA<sub>A</sub> inverse agonist, and an acetylcholinesterase inhibitor, wherein the GABA<sub>A</sub> inverse agonist is selected from the group consisting of:

20 N-n-Butyl-6-chloro-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;  
N-n-Butyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;  
N-(2-Ethylthio)ethyl-6-methoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-  
carboxamide;

N-n-Pentyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

25 N-Benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(2-Tetrahydrofuranyl)methyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-Isoamyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3  
carboxamide:

30 N-(3-Methoxybenzyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide:

N-(3-Ethoxy)propyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-2-(2-Methyl)butyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3

carboxamide;

N-5-Pentanol-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-

carboxamide;

N-Benzyl-6-methoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

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N-(2-Fluorobenzyl)-6-methoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-

carboxamide;

N-(3-Fluorobenzyl)-6-methoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-

carboxamide;

N-(4-Fluorobenzyl)-6-methoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-

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carboxamide;

N-(4/5-Imidazolyl)methyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(3-Thienyl)methyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-

carboxamide;

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N-(2-Tetrahydropyranyl)methyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(2-Fluorobenzyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-

carboxamide;

N-(3,5-Fluorobenzyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-

20

carboxamide;

N-(4-Fluorobenzyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-

carboxamide;

N-(4-Methoxybenzyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-

carboxamide;

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N-(4-Methylbenzyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-

carboxamide;

N-(2-Thienyl)methyl-6-(2-methoxyethoxy)-4-oxo-1,4-tetrahydro-1,5-

naphthyridine-3-carboxamide;

N-(2-Thienyl)methyl-6-morpholino-4-oxo-1,4-tetrahydro-1,5-naphthyridine-

30

3-carboxamide;

N-(2-Thienyl)methyl-6-dimethylamino-4-oxo-1,4-tetrahydro-1,5-

naphthyridine-3-carboxamide;

N-(4-Methylaminomethyl)benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-

naphthyridine-3-carboxamide;

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~~N-[4-(Imidazolylmethyl)benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide,~~

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wherein the GABA<sub>A</sub> inverse agonist and the acetylcholinesterase inhibitor are as defined in claim 1.

13. The method of claim 12, wherein the GABA<sub>A</sub> inverse agonist is N-  
5 Benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide, or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug.

14. The method of claim 12, wherein the acetylcholinesterase inhibitor is  
10 selected from the group consisting of Aricept (donepezil, E2020), Exelon (rivastigmine), metrifonate, galantamine, physostigmine, tacrine, huperzine A, and icopezil, a prodrug thereof, and a pharmaceutically acceptable salt or solvate of said compound or prodrug.

15. The method of claim 12, wherein the acetylcholinesterase inhibitor is  
Aricept (donepezil, E2020) or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug.

16. The method of claim 12, wherein the GABA<sub>A</sub> inverse agonist is N-  
20 Benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide, or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug; and the acetylcholinesterase inhibitor is Aricept (donepezil, E2020) or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug.

17. The method of claim 12, wherein the GABA<sub>A</sub> inverse agonist and the  
acetylcholinesterase inhibitor are administered separately.

18. The method of claim 12, wherein the GABA<sub>A</sub> inverse agonist and the  
30 acetylcholinesterase inhibitor are administered sequentially.

19. The method of claim 12, wherein the GABA<sub>A</sub> inverse agonist and the  
acetylcholinesterase inhibitor are administered simultaneously..

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